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QUANTIFICATION OF THE DIASTOLIC NOTCH IN ULTRASOUND DOPPLER SCREENING OF UTERINE ARTERIES

(Accepted, *Ultrasound in Obstetrics and Gynaecology*)

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ABSTRACT

Objective- To investigate a new method of quantification of the diastolic notch of the flow velocity waveforms of uterine arteries in the prediction of hypertensive disorders of pregnancy.

Methods- Pulsed-wave Doppler was used to obtain Flow Velocity Waveforms (FVWs) from the uterine arteries at 21-22 weeks of gestation from 531 nulliparous women and 94 multiparous women at high risk. From the FVWs, both the Pulsatility Index (PI) and the Notch Index (NI) were calculated and the predictive values for both indices were compared using logistic regression analysis for mild and severe early-onset hypertensive pregnancy complications.

Results- Both the PI and the NI are poor predictors for mild gestational hypertension and pre-eclampsia; predictive values for severe early-onset disease however, were much better. Logistic regression analysis shows the NI has no additional value compared to the PI in the prediction of either mild or severe disease.

Conclusions- The Notch Index offers the possibility to quantify the diastolic notch in uterine artery analysis. Compared to the Pulsatility Index, this does not lead to better predictive values for hypertensive disorders of pregnancy.

INTRODUCTION

In recent years, much research has been done to establish the role of Doppler screening of the uteroplacental circulation in predicting hypertensive disorders of pregnancy and intra-uterine growth retardation[1-8]. The results of these studies, however, have been extremely variable. This can be partly explained by differences in population selection, the site from which Flow Velocity Waveforms (FVWs) were obtained (arcuate vs. uterine arteries) and whether continuous-wave or pulsed wave Doppler was used. Also, the various methods used for analysing the FVWs might have contributed to the difference in results.

The presence of a "diastolic notch" in FVWs of the uteroplacental circulation in pregnancy was first noted by Campbell[9]. A diastolic notch was observed in abnormal FVWs and clearly associated with uteroplacental insufficiency. Fleischer et al.[10] reported better prediction of complications in hypertensive pregnancies when the diastolic notch was used in addition to the S/D ratio. Other investigators have also used the diastolic notch in predicting pre-eclampsia, often in combination with other variables[11-13]. More recently, the "peak systolic over protodiastolic ratio" (AC-ratio) was proposed by Irion et al.[14] as a quantitative substitute for the diastolic notch. The AC-ratio has also been evaluated by North et al[15]. who report similar predictive values for pre-eclampsia and fetal growth retardation compared to the Restistance Index (RI). Bower et al[16] compared the Pulsatility Index (PI) to the AC-ratio and a second index of the notch (D-C)/B, and found that the PI gave the best results.

In the present study we propose a new method for quantifying the diastolic notch. Using this diastolic Notch Index (NI) in both a low-risk group and a high-risk group of pregnant women, we have investigated if this method can improve the predictive power of uterine artery FVWs.

METHODS

Between 1993 and 1995, all outpatients of the antenatal clinic of the Groningen University Hospital who were either healthy nulliparae or multiparae with a history of hypertensive disorder in a previous pregnancy but no current pathology, were asked to enter the study. Five hundred and thirty-one nulliparous healthy pregnant women, and 94 multiparous women with a history of hypertensive disorders in previous pregnancies were recruited. All women had singleton pregnancies, and all measurements took place between 21 and 22 completed weeks of pregnancy. All women gave their informed consent, and the study was approved of by the hospital medical ethics committee.

We used pulsed-wave Colour Doppler ultrasonography (ACUSON 128 XP, Mountainview, California) to obtain FVWs from both uterine arteries in all subjects. To standardise the sample site we used the uterine artery at the crossing with the external iliac artery as previously described[17].

The recorded FVWs were analysed using the Bitpad Plotter System. The Pulsatility Index (PI) was calculated as described by Gosling and King[18]. If a notch was present, a "Notch Index" (NI) was also calculated, as shown in figure 1. The “Notch Index” was derived from the difference between the peak velocity in diastole and the velocity at the nadir of the notch, divided by the mean velocity over one cycle length.

Medical records of all subjects were analysed at least six weeks after delivery. Pregnancy outcome was classified as normal pregnancy, gestational hypertension or pre-eclampsia. In accordance with ISSHP criteria, gestational hypertension was defined as two recordings of diastolic blood pressure of 90 mmHg or higher appearing for the first time after 20 weeks of gestation. Pre-eclampsia was defined as gestational hypertension combined with the presence of proteinuria (defined as 2+ or more on urinalysis sticks) at least once between 20 weeks of gestation and

delivery. Gestational hypertension and pre-eclampsia were further subdivided into “mild” and “severe” according to the following criteria: hypertensive disease was classified as "severe" if there were any of the following complications: intra-uterine growth retardation, intra-uterine death, the HELLP-syndrome, eclampsia, premature birth or placental solution. In all cases of severe hypertensive disease, onset of symptoms was before 35 weeks. All other cases were classified as “mild”. Intra-uterine growth retardation was defined as a birthweight below the 10th percentile for gestational age and sex. Table 1 shows relevant clinical and laboratory data from the various groups.

Analysis of medical records after delivery was kept separate from knowledge of the results of the Doppler measurements. The Doppler results were not given to the patients themselves, nor made available for clinical management.

Predictive values for PI and NI were calculated separately. The test was considered positive if the PI or NI came above the cut-off point in either uterine artery. Values were calculated separately for both study groups for different cut-off points. In addition, logistic regression analysis was used to evaluate the performance of the PI and NI. Statistical tests were carried out at a two-sided significance level of 5%.

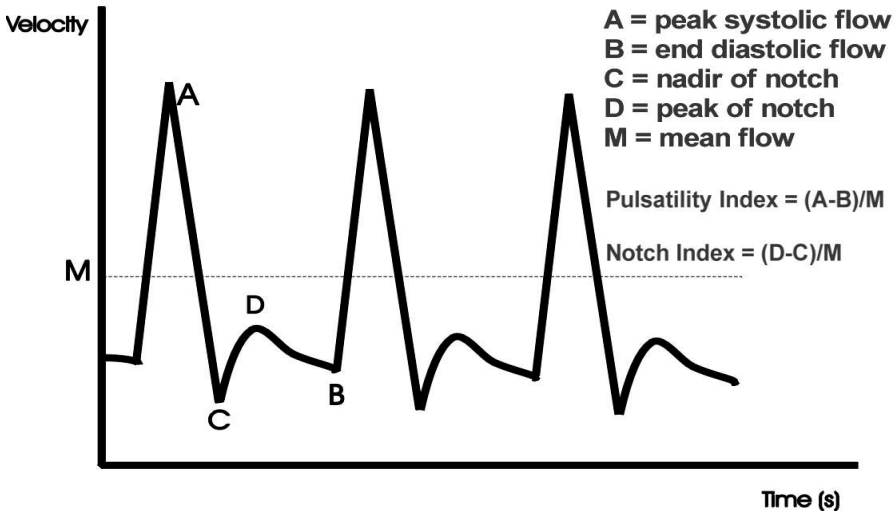

Figure 1. Calculation of the Notch Index.

	Nulliparae (n=531)			Multiparae with pre-eclamspia in previous pregnancy (n=94)		
outcome of present pregnancy	normal pregnancy (n=471)	mild hypertensive disease (n=38)	severe hypertensive disease (n=22)	normal pregnancy (n=63)	mild hypertensive disease (n=19)	severe hypertensive disease (n =12)
diastolic BP (mmHg)	80 *(75-85)*	100* *(95-105)*	100* *(95-105)*	80 *(75-85)*	103* *(100-110)*	103* *(100-105)*
Proteinuria (>300mg/24 hrs or 2+)	25/471 (5%)	5/38 (13%)	7/22 (32%)*	8/63 (13%)	7/19 (37%)*	5/12 (42%)*
Birthweight (grams)	3330 *(2980-3650)*	3455 *(2950-3850)*	2390* *(1880-2550)*	3440 *(3270-3625)*	3568 *(3335-3900)*	1908* *(1475-2680)*
Gestational age at delivery (weeks)	40 *(39-41)*	40 *(39-41)*	37 *(36-40)**	39 *(39-40)*	39 *(39-42)*	35 *(31-38)**
Complications:						
-caesarean section	62/471 (13%)	3/38 (8%)	8/22 (36%)*	5/63 (8%)	1/19 (5%)	7/12 (58%)*
-delivery <37 weeks	46/471 (10%)	0#	10/22 (45%)*	8/63 (13%)	0#	10/12 (83%)*
-birthweight <p10	47/471 (10%)	0#	8/22 (36%)*	5/63 (8%)	0#	5/12 (42%)*
-HELLP- syndrome	0/471 (0%)	0#	4/22 (18%)	0/63 (0%)	0#	2/12 (17%)
-placental abruption	0/471 (0%)	0#	1/22 (5%)	0/63 (0%)	0#	1/12 (8%)
-intra-uterine death	1/471 (0,2%)	0#	1/22 (5%)	0/63 (0%)	0#	1/12 (8%)
-admission to neonatal care unit	73/471 (15%)	5/38 (13%)	7/22 (32%)*	4/63 (6%)	0/19 (0%)	7/12 (58%)*

Table 1. Clinical and laboratory data for the various study groups. All data are median *(interquartile range)* unless noted otherwise. * P < 0.05 , compared to normal pregnancy (Mann-Whitney and Fisher's Exact Test).#: these complications are exclusion criteria for mild hypertensive disease.

RESULTS

Flow velocity waveforms could be obtained from both uterine arteries of all subjects.

A notch was present in one uterine artery in 15 of the 94 subjects from the high-risk group, and in both uterine arteries in 8 subjects; thus, a NI could be calculated in 23 subjects from the high-risk group. In the nulliparous group, a notch was present in one uterine artery in 100 subjects out of 531, and in both uterine arteries in 44 subjects; thus, a NI could be calculated in 144 subjects from this group. Characteristics of the NI in the three pregnancy outcome groups for both study groups are shown in table 2. In both groups, the diastolic notch was significantly more often present in severe hypertensive disease as compared to mild disease and normal pregnancies. Prevalence of the diastolic notch was highest (58%) in those subjects from the high-risk group who again developed severe hypertensive disease.

In those subjects in which a notch was present, the correlation was calculated between the NI and PI using the Spearman non-parametric test, resulting in a correlation coefficient (r) of 0.53 ($P < 0.001$) for the nulliparous group and 0.53 ($P = 0.002$) for the high-risk group.

Both the PI and the diastolic notch are poor predictors of pre-eclampsia in general. There is, however, a great difference between predictive values for mild and severe hypertensive disease. Prediction of mild gestational hypertension and mild pre-eclampsia was poor and not significant; prediction of severe disease, however, was much better, for both PI and NI. Table 3 shows predictive values for the various outcome groups; we chose a cut-off point of 0.03 for the Notch Index and a cut-off point of 1.3 for the PI based on a Receiver Operator Curve (unpublished observations).

Nulliparous (n=531)	*n*	Presence of Diastolic notch (%)	Notch Index (mean) left	right
Uncomplicated pregnancy	471	116 (25%)	0.20	0.17
Mild hypertensive disease				
gestational hypertension	33	16 (48%)*	0.16	0.21
pre-eclampsia	5	0 (0%)	-	-
Severe hypertensive disease	22	12 (55%)*	0.26	0.23
High-risk (n=94)				
Uncomplicated pregnancy	63	12 (19%)	0.15	0.16
Mild hypertensive disease				
gestational hypertension	12	3 (25%)	0.23	0.28
pre-eclampsia	7	1 (14%)	-	-
Severe hypertensive disease	12	7 (58%)*	0.32	0.22

Table 2. Characteristics of the Notch Index in the three outcome groups for both study groups. * $p<0.05$; comparison to uncomplicated pregnancy; Mann-Whitney Test.

NOTCH INDEX (CUT-OFF POINT 0.03)					
Nulliparous (n=531)	N	Se	Sp	LR	*P**
All hypertensive disease	60	47%	75%	5.6	<0.01
*mild					
gestational hypertension	33	49%	75%	10.6	<0.01
pre-eclampsia	5	0%	75%	-	NS
*severe	22	55%	74%	21.0	<0.01
High-risk (n=94)					
All hypertensive disease	31	36%	81%	1.3	NS
*mild					
gestational hypertension	12	25%	81%	1.7	NS
pre-eclampsia	7	14%	81%	1.4	NS
*severe	12	58%	81%	8.3	<0.05

PULSATILITY INDEX (CUT-OFF POINT 1.30)					
Nulliparous (n=531)	N	Se	Sp	LR	*P**
All hypertensive disease	60	45%	78%	4.5	<0.01
*mild					
gestational hypertension	33	24%	78%	3.8	NS
pre-eclampsia	5	0%	78%	-	NS
*severe	22	73%	78%	49.0	<0.01
High-risk (n=94)					
All hypertensive disease	31	45%	68%	1.6	NS
*mild					
gestational hypertension	12	25%	68%	1.7	NS
pre-eclampsia	7	14%	68%	1.2	NS
*severe	12	83%	71%	25.0	<0.01

Table 3. Predictive values for mild and severe hypertensive disease of the Notch Index and Pulsatility Index for both study groups. Se = Sensitivity, Sp = Specificity, LR = Likelihood Ratio; * P calculated by Fisher's Exact Test.

	Nulliparous (n=531)				High-risk (n=94)			
PULSATILITY INDEX	Se	Sp	LR	*P**	Se	Sp	LR	*P**
1.15	77%	66%	52.9	<0.001	92%	66%	50.4	<0.001
1.30	73%	78%	49.0	<0.0001	83%	71%	25.0	<0.001
1.40	64%	83%	34.0	<0.0001	67%	74%	10.8	<0.01
1.50	64%	85%	35.2	<0.0001	58%	79%	8.2	0.010
NOTCH INDEX								
0.03	55%	74%	21.1	<0.01	58%	81%	8.3	<0.01
0.09	55%	75%	21.5	<0.01	58%	81%	8.3	<0.01
0.12	55%	80%	22.6	<0.001	58%	85%	8.8	<0.01
0.14	46%	82%	16.3	<0.01	58%	89%	9.1	<0.001

Table 4. Sensitivity (Se), Specificity (Sp) and Likelihood Ratio (LR) for severe hypertensive disease of the PI and the NI at different cut-off points.

To allow better comparison between NI and PI, we also show predictive values for severe disease in both study groups using different cut-off points of the NI and PI; these values are shown in table 4. For the NI, sensitivity is limited because a notch is not always present; the absence of a notch is defined as a negative test result. The alternative, using NI=0 for a FVW without notch, would result in a positive test result for all subjects, which is not realistic.

The logistic regression analysis was performed with logarithmically transformed PI and NI (the distribution of PI is well approximated by the lognormal distribution). The analysis revealed a significant effect of the PI ($P<0.001$) for the outcome variable "severe hypertensive disease" but no additional effect of the NI. When considered alone, without the PI, the NI was significantly related to outcome. We also performed the regression analysis with the outcome defined as presence of absence of at least mild disease. The results were similar: the NI did not significantly improve the predictive power of the PI.

DISCUSSION

In this article we have introduced the Notch Index, a method to quantify the diastolic notch in the analysis of uterine artery Flow Velocity Waveforms. In contrast to earlier proposed methods to quantify the notch[14-16], the Notch Index incorporates a correction for mean flow (Figure 1). We investigated the prediction of mild and severe hypertensive disorders by the NI compared to the PI in both a (high-risk) group of women with a history of hypertensive disease in pregnancy and a (low-risk) group of nulliparous pregnant women.

In those subjects in whom a diastolic notch was present, there was a significant positive correlation between the Notch Index and Pulsatility Index. The NI, as well as the PI, reflects the amount of impedance to blood flow distal to the uterine artery. The correlation between NI and PI is however not as strong as would be expected if they were both dependent only on impedance to blood flow. This is consistent with the observation that even in abnormal FVWs with a very high PI, a diastolic notch is not always present. Talbert[19] used a computer model to investigate the relationship between vessel resistance, vessel compliance and FVWs in uterine arteries. His findings indicated that the diastolic notch depended mainly on vessel wall compliance, whereas the PI is determined by vascular resistance distal to the uterine artery.

Some of the variables calculated from FVWs are the systolic/diastolic ratio, the Resistance Index, and the Pulsatility Index. So far, a major disadvantage of the use of the diastolic notch as a variable was always that it was dichotomous; it is either present or absent, and in contrast to the other (numeric) variables mentioned above, it was not possible to set a "cut-off point" to match the sensitivity one aims to achieve. To overcome this problem, we have introduced the Notch Index and compared its predictive power to the uterine artery Pulsatility Index.

Both the Pulsatility Index and the Notch Index are predictors of poor pregnancy outcome associated with severe hypertensive disorders of pregnancy. In this study we found better predictive values for the PI compared to the NI; this is in contrast to some earlier studies[11-13].

One possible explanation for this discrepancy is our use of the PI where most of the other investigators used the Resistance Index (RI).

In conclusion, quantification of the diastolic notch did not improve predictive power of uterine artery screening. In our study as well as others, uterine artery screening shows disappointing predictive values for mild gestational hypertension and pre-eclampsia. It does however reach good predictive values for severe pre-eclampsia and gestational hypertension associated with poor pregnancy outcome. The finding that neither the NI nor the PI of uterine arteries predicts the occurrence of mild hypertensive disease in pregnancy indicates that insufficient dilatation of the spiral arteries may not be a causal factor here. In this respect our findings support the current concept of the heterogeneous causes of pre-eclampsia[20].

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